Beta-Blockers

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
acebutolol (Sectral®)[1]	generic	HTN Ventricular arrhythmias
atenolol (Tenormin®)[2]	generic	Angina pectoris HTN MI
betaxolol[3]	generic	HTN
bisoprolol (Zebeta®)[4]	generic	HTN
carvedilol (Coreg®)[5]	generic	Mild to severe HF, to reduce the risk of hospitalization and improve survival HTN Reduce risk of death following MI with Left Ventricular Dysfunction (LVD) in patients with or without HF symptoms
carvedilol (Coreg CR®)[6]	GSK	
labetalol[7]	generic	HTN
metoprolol tartrate (Lopressor®)[8]	generic	Angina pectoris HTN MI
metoprolol succinate ER (Toprol XL®)[9]	generic	Angina pectoris HF – New York Heart Association (NYHA) Class II or III HTN
nadolol (Corgard®)[10]	generic	Angina pectoris HTN
nebivolol (Bystolic™)[11]	Forest Pharm	HTN
pindolol[12]	generic	HTN
propranolol[13]	generic	Angina pectoris Cardiac arrhythmias Essential tremor HTN Hypertrophic subaortic stenosis Migraine prophylaxis MI Pheochromocytoma
propranolol (Hemangeol™)[14]	Pierre Fabre	Proliferating infantile hemangioma requiring systemic therapy
propranolol ER (Innopran XL®)[15]	Akrimax Pharm	HTN
propranolol ER (Inderal® XL)[16]	Mist Pharm	HTN
propranolol LA (Inderal® LA)[17]	generic	Angina pectoris HTN Hypertrophic subaortic stenosis Migraine prophylaxis
sotalol (Betapace®)[18]	generic	Ventricular arrhythmias
sotalol (Betapace AF™)[19]	generic	Maintenance of normal sinus rhythm in atrial fibrillation/flutter
sotalol (Sotylize™)[20]	Arbor	Ventricular arrhythmias Maintenance of normal sinus rhythm in atrial fibrillation/flutter
timolol[21]	generic	HTN Migraine prophylaxis MI

HTN = hypertension; MI = myocardial infarction; HF = heart failure

Beta-Blocker Combinations with Diuretics

Drug	Manufacturer	FDA-Approved Indication
atenolol / chlorthalidone (Tenoretic®)[22]	generic	HTN
bisoprolol / hydrochlorothiazide (Ziac®)[23]	generic	HTN
metoprolol succinate / hydrochlorothiazide (Dutoprol™)[24]	AstraZeneca	HTN
metoprolol tartrate / hydrochlorothiazide (Lopressor® HCT)[25]	generic	HTN
nadolol / bendroflumethiazide (Corzide®)[26]	generic	HTN
propranolol / hydrochlorothiazide[27]	generic	HTN

These combination products are not indicated for initial therapy of HTN.

OVERVIEW

Beta-blockers are approved for a variety of conditions. This review will focus on the following cardiovascular (CV) uses of beta-blockers: hypertension, heart failure, angina, myocardial infarction, and cardiac arrhythmias.

Hypertension

Hypertension (HTN) affects over 30 percent of adult Americans and only half of this population has their hypertension under control. From 1999 to 2009, the death rate from heart disease declined 32.7 percent, but inpatient cardiovascular operations and procedures increased by 28 percent from 2000 to 2010. Hypertension is an independent risk factor for the development of cardiovascular disease (CVD).[28] The more elevated the blood pressure, the higher the risk of myocardial infarction (MI), stroke, heart failure, and kidney disease.[29] To reduce the risk of cardiovascular (CV) events, the current blood pressure goal is less than 140/90 mm Hg.[30] The American Diabetes Association (ADA) suggests that the blood pressure goal for many people with diabetes and hypertension should be <140 mmHg systolic and <80 mmHg diastolic, but that lower systolic targets (such as <130 mmHg) may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden.[31] For patients with chronic renal disease, the current goal for blood pressure therapy is less than 130/80 mm Hg.[32] For patients with known coronary artery disease (CAD) or CAD equivalent, stable angina, unstable angina (UA)/non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), the target blood pressure is also less than 130/80 mm Hg.[33] Attainment of blood pressure goals results in a reduced risk of CV events.[34] There is inter-patient variability in response to various antihypertensive classes. In the absence of compelling indications, reaching target blood pressure is central in determining CV benefit in patients with hypertension, not the specific agent used.[35,36,37,38]

A number of trials, including STOP-Hypertension-2, NORDIL, and INVEST, showed little difference in overall outcomes for beta-blockers and diuretics versus ACE inhibitors and calcium channel blockers (CCBs).[39,40,41] The ASCOT-BPLA and LIFE trials showed that the beta-blocker atenolol had an increased rate of CVD and death compared to the CCB amlodipine.[42,43]

Most beta-blockers are indicated for the treatment of HTN. Beta-blockers appear to have similar efficacy in the treatment of hypertension.[44,45,46,47] The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8), published in 2014, recommends first-line therapy for HTN in the non-black population as a thiazide-type diuretic,

calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) and a thiazide diuretic or CCB in the black population. Beta-blockers were not recommended as initial treatment of hypertension. This is due to use in a study which resulted in a higher rate of the primary composite outcome of CV death, MI, or stroke compared to use of an ARB, a finding that was driven largely by an increase in stroke.[48]

The 2014 hypertension science advisory by the American Heart Association (AHA), American College of Cardiology (ACC), and the Centers for Disease Control and Prevention (CDC) recommend that lifestyle modifications should be initiated in all patients with hypertension and the medication choice depends on the patient's blood pressure level. For patients with certain co-morbid conditions, specific medications should be considered first-line treatments.[49] Beta blockers are one of the classes suggested in patients with coronary artery disease, post MI, HF, and diabetes.

Since the publication of the prior JNC-7 and ADA guidelines for the treatment of hypertension, a meta-analysis aimed at evaluating the blood pressure lowering effects and incidences of heart attack, stroke, and death in patients taking HCTZ has been published.[50] Based on 14 studies, including 1,234 patients taking HCTZ, blood pressure lowering with HCTZ was inferior to all other classes, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium antagonists. Additionally, the meta-analysis concluded that there are no studies or evidence that HCTZ reduces myocardial infarction, stroke, or death.

The role of beta-blockers as initial therapy, particularly in the absence of these compelling indications, for hypertension has been questioned.[51] It has been shown that beta-blockers have similar efficacy in MI patients versus placebo or other drugs, reduced risk of stroke compared to placebo, but are less effective than other drugs against stroke, particularly in the elderly.[52,53,54] Cochrane database reviews showed beta-blockers to be inferior to calcium channel blockers for all-cause mortality, stroke, and total CV events and to be inferior to angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for stroke. Beta-blockers as first-line for hypertension have also been shown to be inferior to low-dose thiazides as first-line for hypertension, in reducing CHD and mortality.[55,56] It should be noted that the majority of the data are from trials involving atenolol. The 2011 National Institute for Health and Clinical Excellence (NICE) Guidelines no longer prefer beta-blockers as routine initial therapy for hypertension.[57] In NICE, the use of thiazide-type diuretics with beta-blockers is not recommended due to the increased risk for development of diabetes. In diabetic patients, beta-blockers have been shown to reduce the risk of cardiovascular disease (alternatives include thiazide diuretics, CCBs, ACE inhibitors, and ARBs).[58] African American patients generally have a suboptimal response to beta-blockers in blood pressure reduction compared to diuretics and CCBs; however, they still benefit from the reduction of risk from clinical outcomes when the same blood pressure reduction is achieved. Nebivolol has shown efficacy in reducing blood pressure in African Americans.[59]

Heart Failure

Heart failure (HF) affects over five million patients in the United States.[60] Despite combination therapy with angiotensin converting enzyme (ACE) inhibitors, diuretics, and digoxin, five-year mortality rates remain high. The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for the Diagnosis and Management of Heart Failure in the Adult identify four stages of HF recognizing both the development and progression of the disease. Patients in stages A and B are considered at risk for HF. Stage C are patients with structural heart disease with reduced left ventricular ejection fraction (LVEF) with prior or current symptoms of HF. Stage D patients have

refractory HF requiring specialized interventions. For Stage B, beta-blockers and ACE inhibitors should be used in all patients with a recent history of MI regardless of EF or presence of HF. Beta-blockers and ACE inhibitors are also recommended in patients without a history of MI, with a reduced EF, and no HF symptoms. For Stage C, these guidelines recommend diuretics and salt restriction in patients with evidence of fluid retention, ACE inhibitors in all patients, unless contraindicated, and one of three beta-blockers (bisoprolol, carvedilol, or metoprolol succinate extended-release) for all stable patients, unless contraindicated. An angiotensin receptor blocker (ARB) may be used in ACE inhibitor-intolerant patients and is considered a reasonable alternative.[61,62]

The two beta-blockers with the FDA-approved indication for HF are metoprolol succinate extended-release (Toprol XL), a beta1-selective (cardioselective) adrenergic antagonist, and carvedilol (Coreg and Coreg CR), a combined alpha- and non-selective beta-blocker.[63,64,65] Bisoprolol (Zebeta) is a cardioselective beta-blocker that has been studied in HF; however, bisoprolol is not FDA-approved for this indication.

Bisoprolol, metoprolol succinate ER, and carvedilol have been shown to reduce symptoms of HF and improve clinical status and patients' well-being plus reduce the risk of death and the combined risk of death and hospitalization.[66] All three drugs have been shown to reduce mortality and hospitalization by 30 to 40 percent, in HF.[67,68,69,70,71,72] There have been many placebo-controlled trials of beta-blockers in patients with systolic dysfunction already treated with the standard therapy of diuretics and ACE inhibitors. The COMET trial showed reduced mortality and vascular events with carvedilol versus metoprolol.[73,74]

Angina Pectoris

The American College of Cardiology/American Heart Association (ACC/AHA) chronic stable angina 2007 focused update of the original 2002 guidelines recommend beta-blockers and/or ACE inhibitors with the addition of other drugs, as needed, for blood pressure control in patients with CAD.[75] The 2007 guidelines recommend initiating and continuing beta-blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome (ACS), or left ventricular dysfunction (LVD), with or without heart failure symptoms, unless contraindicated.[76]

Beta-blockers appear to have similar efficacy in stable angina. Beta-1 selective agents without intrinsic sympathomimetic activity (ISA) are used most frequently.[77] Beta-blockers are able to improve exercise capacity and decrease frequency of angina episodes.[78] The cardioselective beta-blockers block the beta-1 receptor and have less inhibition of the peripheral vasodilation and bronchodilation induced by the beta-2 receptors. At higher doses, cardioselectivity may be lost. Beta-blockers with ISA may not decrease heart rate and blood pressure at rest, so these agents should be avoided in patients with a prior MI or HF who benefit from beta blockade. However, since it is the reduction in exercise heart rate that is of primary importance, the ISA beta-blockers can still be effective.

Acute MI (UA/NSTEMI and STEMI)

Beta-blockers prevent recurrent ischemia, life-threatening ventricular arrhythmias, and improve survival in patients with prior MI.[79,80] The 2014 ACC/AHA guidelines for Non-ST Coronary Syndromes and the ACCF/AHA 2013 STEMI guidelines recommend indefinite beta-blocker therapy in all patients without a contraindication, with UA and NSTEMI, collectively referred to as non-ST elevation ACS, and STEMI.[81,82,83] The 2014 AHA scientific statement on the treatment of hypertension in ischemic heart

disease support these recommendations in hemodynamically stable patients and prefer use of cardioselective beta-blockers without ISA.[84]

Cardiac Arrhythmia

Patients with arrhythmia have a higher risk of total mortality, coronary heart disease mortality, and sudden cardiac death.[85] Ventricular arrhythmias can occur in patients with heart failure, as well as with MI.[86,87,88] Ventricular arrhythmias contribute to the increased risk for sudden cardiac death in patients with HF and MI.[89,90,91,92,93] Beta-blockers improve survival in patients who have had a MI as they are able to reduce the incidence of sudden cardiac death.[94,95] The ACC/AHA/ESC 2006 guidelines for the management of patients with ventricular arrhythmias and prevention of sudden cardiac death consider beta-blockers to be safe and effective and the mainstay of antiarrhythmic drug therapy.[96]

PHARMACOLOGY[97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117]

Beta-blockers are able to improve exercise capacity, decrease frequency of angina episodes, and reduce exercise-induced ST depression. The beneficial effect of beta-blockers in post-MI patients is related to resting HR reduction.[118] Beta-blockers inhibit the adverse effects of the sympathetic nervous system (SNS) in heart failure patients. Although cardiac adrenergic drive initially supports the performance of the failing heart, long-term activation of the SNS exerts deleterious effects. These effects include increased ventricular volumes and pressures, cardiac hypertrophy, provocation of arrhythmias, and apoptosis. Beta-blockers antagonize SNS activation, minimize damage, and, ultimately, slow disease progression.

The catecholamines, norepinephrine and epinephrine, are mediated by beta and alpha receptors. Beta-blockers bind to adrenergic receptors to competitively inhibit catecholamines, resulting in inhibition of vasoconstriction, chronotropic, and inotropic activity. Cardioselective beta-blockers are beta-1 selective resulting in decreased heart rate and contractility. Nonselective beta-blockers have equal affinity for both beta-1 and beta-2 receptors. Inhibition of beta-2 receptors causes bronchoconstriction and vasoconstriction. At higher doses, cardioselective agents can also block beta-2 adrenergic receptors. Nebivolol (Bystolic) is beta-1 selective at doses ≤ 10 mg or in extensive metabolizers (majority of the population), but it loses cardioselectivity at doses above 10 mg and in poor metabolizers. Beta-blockers with alpha-adrenergic activity block alpha-1 receptors resulting in decreased peripheral and coronary vascular resistance. Beta-blockers with ISA, also called partial agonist activity, have low-grade beta stimulation at rest.

Intrinsic sympathomimetic activity (ISA) characterizes a group of beta blockers that are able to stimulate beta-adrenergic receptors (agonist effect) and to oppose the stimulating effects of catecholamines (antagonist effect) in a competitive way. The presence of ISA results in less resting bradycardia and less reduction in cardiac output than is observed with beta blockers without ISA.[119]

The thiazide (bendroflumethiazide, hydrochlorothiazide) and thiazide-like diuretics (chlorthalidone) block the reabsorption of sodium and chloride leading to diuresis and a reduction in intravascular volume. Consequently, there are increases in plasma renin activity and aldosterone secretion. Concurrent administration of an angiotensin II receptor antagonist and a thiazide diuretic may help to decrease potassium loss that occurs with thiazide diuretic therapy.[120,121]

Pharmacologic Properties

Drug	Cardioselective	ISA	Vasodilatory
acebutolol	Y	Y	--
atenolol	Y	--	--
betaxolol	Y	--	--
bisoprolol	Y	--	--
carvedilol	--	--	Y (alpha-1 antagonist)
carvedilol CR (Coreg CR)	--	--	Y (alpha-1 antagonist)
labetalol	--	--	Y (alpha-1 antagonist)
metoprolol tartrate	Y	--	--
metoprolol succinate ER	Y	--	--
nadolol	--	--	--
nebivolol (Bystolic)	Y	--	Y (nitric oxide pathway)
pindolol	--	Y	--
propranolol	--	--	--
propranolol ER (Innopran XL)	--	--	--
propranolol ER (Inderal XL)	--	--	--
propranolol LA	--	--	--
sotalol	--	--	--
sotalol AF	--	--	--
timolol	--	--	--

PHARMACOKINETICS

Drug	Bioavailability (%)	Half-life (hrs)*	Metabolism	Excretion (%)
acebutolol[122]	40	3-4	1 active metabolite (diacetolol)	Urine: 30-40
atenolol[123]	50	6-7	Negligible hepatic metabolism	Urine: 50
betaxolol[124]	89	14-22	Inactive metabolites	Urine
bisoprolol[125]	80	9-12	Inactive metabolites	Urine
carvedilol[126]	25-35 (Cmax reduced in presence of food)**	7-10	3 weakly active metabolites via CYP2D6 and CYP2C9	Primarily Feces
carvedilol CR (Coreg CR)[127]	25-35 (Cmax reduced in the fasting state)***	5-11	3 weakly active metabolites via CYP2D6 and CYP2C9	Primarily Feces; less than 7% in the urine
labetalol[128]	25	6-8	Hepatic via glucuronidation	Urine: 55-60 as glucuronide conjugates
metoprolol succinate/ER[129,130]	50	3-7	Inactive metabolites via CYP2D6	Predominantly urine
nadolol[131]	30	20-24	None	Urine
nebivolol (Bystolic)[132]	12-96	12-19	Hepatic: active metabolites via CYP2D6 and glucuronidation	Urine: 38 Feces: 44
pindolol[133]	--	3-4	Hepatic (60%) to metabolites	Urine: 35-40 Feces: 6-9
propranolol[134]	30-40	3-6	4 active metabolites via CYP2D6 and CYP1A2	Urine: 96-99
propranolol ER (Innopran XL)[135]	25	8-11	4 active metabolites via CYP2D6 and CYP1A2	Urine
propranolol ER (Inderal XL)[136]	25	8	4 active metabolites via CYP2D6 and CYP1A2	Urine
propranolol LA[137]	25	8-11	4 active metabolites via CYP2D6 and CYP1A2	Urine
sotalol/AF[138,139,140]	90-100	12	None	Urine
timolol[141]	50	4	Hepatic to inactive metabolites	Urine

* Half-life of beta-blockers does not directly correlate with the duration of activity.

** Because the presence of food in the gut reduces the maximum concentration (Cmax) of carvedilol, it is recommended that this drug be taken with food to minimize the risk for hypotension.[142]

*** The AUC and Cmax of carvedilol controlled-release (Coreg CR) are decreased when given in a fasting state; therefore, carvedilol controlled-release (Coreg CR) should be administered with food to enhance absorption.[143]

Metabolizers of CYP2D6 (e.g., carvedilol, metoprolol, nebivolol, and propranolol) are subject to the effects of genetic polymorphism. The majority of the population is extensive metabolizers (EMs) and a minority is poor metabolizers (PMs) of CYP2D6. Poor metabolizers exhibit higher plasma concentrations compared to extensive metabolizers.

CONTRAINDICATIONS/WARNINGS[144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163]

Abrupt discontinuation of or hypersensitivity to beta-blocker therapy, acute bronchospasm, cardiogenic shock, sick sinus syndrome (unless a permanent pacemaker is in place), advanced (greater than first degree) atrioventricular (AV) block, severe bradycardia, decompensated cardiac failure, anuria, and acute pulmonary edema are considered contraindications for use of beta-blockers.

In general, patients with bronchospastic diseases should not receive beta-blockers. Carvedilol, propranolol, and sotalol, are contraindicated in patients with asthma and related bronchospastic conditions. Metoprolol succinate ER may be used with extreme caution in patients with bronchospastic disease, such as asthma, who do not respond or can not tolerate other antihypertensives. Since beta1-selectivity is not absolute, a beta2-stimulating agent should be administered concomitantly, and the lowest possible dose of metoprolol succinate ER should be used.

A Cochrane systematic review found that cardioselective beta-blockers in COPD patients were not related to respiratory adverse effects.[164] It should be noted that several of the included studies were single-dose studies or for short durations.

In diabetic patients, beta-blockers can mask some of the symptoms of hypoglycemia, particularly tachycardia. Other symptoms of hypoglycemia, such as dizziness or sweating, may not be significantly affected by beta-blocker therapy.

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia.

Patients with peripheral arterial disease (PAD) may experience worsening of symptoms on beta-blocker therapy. Beta-blockers may also mask tachycardia associated with hyperthyroidism. Abrupt beta-blocker withdrawal may be associated with an exacerbation of symptoms of hyperthyroidism and may precipitate thyroid storm.

Initiation of high-dose metoprolol extended-release should be avoided in patients undergoing non-cardiac surgery; use in patients with CV risk factors has been associated with bradycardia, hypotension, stroke, and death. Chronic beta-blocker therapy should not be routinely withdrawn prior to major surgery. However, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Caution should be exercised when amide anesthetics (e.g., lidocaine, bupivacaine, mepivacaine) are administered concomitantly with propranolol.

Beta-blockers should generally be avoided in vasospastic (Prinzmetal's) angina. In patients with pheochromocytoma, an alpha-blocking agent should be initiated prior to the use of any beta-blocker.

Propranolol (Hemangeol) oral solution is contraindicated in premature infants with corrected age less than five weeks and in infants weighing less than two kg. Do not use Hemangeol in patients who are not able to feed or are vomiting.

Sotalol is contraindicated in congenital or acquired long QT syndromes, baseline QT interval >450 msec, cardiogenic shock, hypokalemia (<4 mEq/L), or creatinine clearance <40 mL/min.

Sotalol can cause serious ventricular arrhythmias, primarily Torsades de Pointes (TdP) type ventricular tachycardia, associated with QT interval prolongation. QT interval prolongation is directly related to the dose of sotalol. Factors such as reduced creatinine clearance, gender (female), and larger doses increase the risk of TdP. The risk of TdP can be reduced by adjustment of the sotalol dose according to creatinine clearance and by monitoring the ECG for excessive increases in the QT interval.

In single-dose studies, patients with cirrhosis have been reported to have significantly higher concentrations of carvedilol (four- to seven-fold) compared to healthy patients. Patients with severe liver disease should not receive carvedilol. Nebivolol (Bystolic) is contraindicated in severe hepatic impairment (Child-Pugh > B). Nebivolol should be used with caution in patients with moderate hepatic impairment. Propranolol, metoprolol, labetalol, acebutolol, and timolol should be used with caution in patients with impaired hepatic function. Bisoprolol should be used with caution in hepatic impairment and the dose adjusted. Pindolol should be used with caution in severe hepatic impairment and the dose adjusted. Thiazide diuretics should be used with caution in patients with impaired hepatic function, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Nebivolol should be used with caution in patients with severe renal impairment. Propranolol, nadolol, atenolol, and pindolol should be used with caution in patients with impaired renal function. Sotalol, acebutolol, and betaxolol should also be used with caution in patients with impaired renal function and the dose adjusted. Bisoprolol should be used with caution in patients with CrCl less than 40 mL/min and the dose adjusted. The dose of timolol should be adjusted in patients with CrCl < 10 mL/min. Thiazide diuretics are not recommended in patients when CrCl is ≤ 30 mL/min.

Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in some patients treated with alpha-1 blockers.

Hydrochlorothiazide has been reported to cause acute transient myopia and acute angle-closure glaucoma. Symptoms such as decreased visual acuity or ocular pain can occur within hours to weeks of drug initiation and, if untreated, can lead to permanent vision loss. Hydrochlorothiazide should be discontinued as rapidly as possible. Prompt medical or surgical treatments may be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

DRUG INTERACTIONS [165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185]

Both digitalis glycosides and beta-blockers slow AV conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia. Amiodarone can increase beta-blocker levels; therefore, the combination should be used with caution. Co-administration of amiodarone and carvedilol has been shown to increase concentrations of the S-enantiomer of carvedilol by two-fold. Therefore, patients should be observed for signs of bradycardia and heart block. Beta-blockers may potentiate rebound HTN after discontinuation of clonidine.

Verapamil and, to a lesser degree, diltiazem can potentiate the cardiac depressant effect of beta-blockers (potentially leading to bradycardia or heart block). Beta-blockers should be used with caution in combination with these agents.

The CYP2D6 enzyme is one of the enzymes that metabolize carvedilol, metoprolol, propranolol, timolol, and nebivolol (Bystolic). Strong inhibitors of CYP2D6, such as fluoxetine, quinidine, paroxetine, and propafenone, will cause the beta-blocker concentrations to increase. There will be an increased risk of adverse effects and a reduction in the cardioselectivity of metoprolol.

Beta-blockers, when given with catecholamine-depleting drugs such as monoamine oxidase (MAO) inhibitors and reserpine, may cause an exaggerated hypotensive response, such as vertigo, syncope, and postural hypotension. Monitoring for hypotension, bradycardia, vertigo, syncope, and postural hypotension should be performed. Concurrent administration with clonidine has been reported to potentiate the hypotensive effects and worsening of bradycardia.

Cyclosporine levels have been reported to increase with concurrent carvedilol therapy. Monitoring of cyclosporine levels and possible reduction in the cyclosporine dosage may be necessary.

Rifampin, a strong CYP 450 enzyme inducer, has been reported to reduce the bioavailability of carvedilol by 70 percent.

Sotalol/AF can increase levels of adenosine and other antiarrhythmic agents. The combination of diuretics and sotalol should be used with caution due to electrolyte imbalance.

Beta-blockers should not be used with the diagnostic agent, methacholine.

In general, diuretics should not be given with lithium, since they can reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Non-steroidal anti-inflammatory agent (NSAIDs) can reduce the diuretic, natriuretic, and antihypertensive effects diuretics.

ADVERSE EFFECTS[186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206]

Adverse effects in HTN patients, and for sotalol/AF in ventricular tachycardia/ventricular fibrillation patients, are listed below.

Drug	Hypotension/ Postural Hypotension	Syncope	Dizziness/Vertigo	Bradycardia
acebutolol	2	nr	6	2
atenolol	2-4	reported	2-13	3
betaxolol	reported	<2	4.5-14.8	5.8-8.1
bisoprolol	reported	reported	2.9-3.5	0.4-0.5
carvedilol (Coreg, Coreg CR)	2	reported	5	2
labetalol	1	reported	11	0
metoprolol succinate/ER (Toprol XL)	0.1	0.1	0.1	0.3
nadolol	0.1	nr	0.2	0.2
nebivolol (Bystolic)	nr	reported	2-4	0-1
pindolol	reported	nr	reported	reported
propranolol/LA	reported	nr	reported	reported
propranolol ER (Innopran XL)	reported	nr	4-7	reported
propranolol ER (Inderal XL)	reported	nr	4-7	reported
sotalol/AF	reported-6	reported-5	13.1-20	12.3-16
timolol	reported	nr	reported	reported

Adverse effects are indicated as percentage occurrence. Adverse effects data are compiled from package inserts and cannot be considered comparative or all inclusive. nr = not reported

Sotalol/AF can cause serious ventricular arrhythmias, primarily Torsades de Pointes type ventricular tachycardia (associated with QT interval prolongation).

A meta-analysis of 15 trials with beta-blockers evaluated the risks of depression, fatigue, and sexual dysfunction.[207] For depressive symptoms, seven trials with over 10,000 patients found there was no difference in the frequency of depressive symptoms in patients taking beta-blockers compared to those on placebo. In ten trials with over 17,000 patients, fatigue was more frequently reported in patients taking beta-blockers. Older beta-blockers were more commonly associated with complaints of fatigue. In six trials with almost 15,000 patients, beta-blockers had slightly more reports of sexual dysfunction than placebo.

Adverse effects of beta-blockers in HF patients were evaluated in an analysis.[208] Beta-blockers were associated with the increased risk of hypotension (11 per 1,000; 95% CI, 0 to 22), dizziness (57 per 1,000; 95% CI, 11 to 104), and bradycardia (38 per 1,000; 95% CI, 21 to 54). Fatigue was not associated with beta-blockers. Beta-blockers were associated with a reduction in all-cause withdrawal from therapy (14 per 1,000; 95% CI, -2 to 29), lower all-cause mortality (34 per 1,000; 95% CI, 20 to 49), HF hospitalizations (40 per 1,000; 95% CI, 22 to 58), and worsening HF (52 per 1,000; 95% CI, 10 to 94).

In clinical trials of primarily mild to moderate HF with immediate-release carvedilol, hypotension and postural hypotension occurred in 9.7 percent and syncope in 3.4 percent of patients compared to 3.6 percent and 2.5 percent of placebo patients, respectively. The risk for these events was highest during the first 30 days of dosing, corresponding to the up-titration period.[209]

In propranolol (Hemangeol) trials, the most frequently reported adverse events (occurring ≥ 10 percent of patients) were sleep disorders, aggravated respiratory tract infections, diarrhea, and vomiting.

SPECIAL POPULATIONS[210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226, 227, 228,229,230]

Pediatrics

Safety and effectiveness of the beta-blockers in children have not been established, except for metoprolol ER (Toprol XL) and propranolol (Hemangeol). Many of the agents have been used in children; however, clinical trial data are lacking. Safety and effectiveness of propranolol (Hemangeol) for infantile hemangioma have not been established in pediatric patients greater than one year of age.

In patients six years and older with hypertension, metoprolol succinate ER is given 1 mg/kg once daily. The maximum initial dose is 50 mg/day. The dose should be adjusted based on blood pressure response. Doses above 2 mg/kg/day or 200 mg/day have not been studied.

A randomized four-week trial of metoprolol succinate ER in 144 hypertensive children, ages six to 16 years, showed lowering of both systolic and diastolic blood pressure with no serious adverse events.[231] However, this study did not meet its primary endpoint of dose response for reduction in systolic blood pressure.

Pregnancy

Acebutolol, pindolol, and sotalol are Pregnancy Category B. Atenolol is Pregnancy Category D. The other beta-blockers in this review are Pregnancy Category C.

Other

Beta blockers have been used for hypertension, but evidence for a benefit in the elderly has not been convincing. They may have a role in combination therapy, especially with diuretics. Beta blockers are indicated in the treatment of elderly patients who have hypertension with CAD, HF, certain arrhythmias, migraine headaches, and senile tremor.[232] When switching elderly patients from higher doses of immediate-release carvedilol (12.5 mg or 25 mg twice daily) to controlled-release carvedilol (Coreg CR), a lower starting dose of controlled-release carvedilol should be considered to minimize the potential for syncope, dizziness, or hypotension.[233,234]

Nebivolol (Bystolic) was studied in a randomized, double-blinded, placebo-controlled, multicenter trial of 300 African American patients with mild to moderate hypertension.[235] Nebivolol given once daily over 12 weeks significantly reduced both SBP at doses of 10 mg to 40 mg ($p \leq 0.044$) and DBP at doses of 5 mg to 40 mg ($p \leq 0.004$). There were no significant differences in adverse events compared to placebo. Nebivolol reduced blood pressure in African Americans who typically do not respond to beta-blockers, as well as Caucasians. However, nebivolol has not been compared to other beta-blockers in the African American population.

Nebivolol was also studied in an eight-week randomized, double-blind, placebo-controlled trial of 277 self-identified Hispanics with stage I-II hypertension.[236] The starting dose of nebivolol was 5 mg/day titrated at two-week intervals to 10, 20, or 40 mg/day, as needed to achieve DBP control. Nebivolol resulted in significant mean reductions in both trough-seated DBP and systolic blood pressure (SBP); (DBP: -11.1 mm Hg versus -7.3 mm Hg, p<0.0001; SBP: -14.1 mm Hg versus -9.3 mm Hg; p=0.001). Adverse events occurred in 17 percent of nebivolol and 22 percent of placebo patients.

Due to the increased risk of QT interval prolongation, treatment with sotalol/AF must be started only in patients observed for a minimum of three days on their maintenance dose in a facility that can provide electrocardiographic (ECG) monitoring and in the presence of personnel trained in the management of serious ventricular arrhythmias.

DOSAGES[237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257]

Drug	Hypertension	Angina Pectoris	Heart Failure	Other Indications	Availability
acebutolol	200-400 mg twice daily	-	-	See package insert for other indications	200, 400 mg capsule
atenolol	50-100 mg daily	50-200 mg daily	-	MI: 50 mg twice daily or 100 mg daily	25, 50, 100 mg tablets
betaxolol	10-20 mg daily	-	-	-	10, 20 mg tablets
bisoprolol	2.5-20 mg daily	-	-	-	5, 10 mg tablets
carvedilol	6.25-25 mg twice daily	-	3.125 - 25 mg twice daily	LVD following MI: 3.125–25 mg twice daily	3.125, 6.25, 12.5, 25 mg tablets
carvedilol CR (Coreg CR)	20–80 mg once daily	-	10–80 mg once daily	LVD following MI: 20-80 mg once daily	10, 20, 40, 80 mg capsules
labetalol	100-400 mg twice daily	-	-	-	100, 200, 300 mg tablets
metoprolol tartrate	100-450 mg daily	50 mg twice daily to 400 mg daily	-	MI: 25-50 mg every 6 hours, then 100 mg twice daily	25, 50, 100 mg tablets
metoprolol succinate ER	25-400 mg daily	100-400 mg daily	12.5-200 mg daily	-	25, 50, 100, 200 mg tablets
nadolol	40-320 mg daily	40-240 mg daily	-	-	20, 40, 80 mg tablets
nebivolol (Bystolic)	5-40 mg daily	-	-	-	2.5, 5, 10, 20 mg tablets
pindolol	5 mg twice daily to 60 mg daily	-	-	-	5, 10 mg tablets
propranolol	40 mg twice daily initially, then 120-240 mg/day in divided doses	80-320 mg daily in divided doses	-	See package insert for other indications	10, 20, 40, 60, 80 mg tablets; 20 mg/5 ml, 40 mg/5 ml solution

Dosages (continued)

Drug	Hypertension	Angina Pectoris	Heart Failure	Other Indications	Availability
propranolol (Hemangeol)	-	-	-	Infantile hemangioma: initiate at ages 5 weeks to 5 months at 0.15 mL/kg (0.6 mg/kg) twice daily; adjust to maintenance dose of 0.4 mL/kg (1.7 mg/kg) twice daily; administer at least 9 hours apart during or after feeding; monitor heart rate and blood pressure for 2 hours after the first dose or increasing dose.	4.28 mg/mL oral solution (120 mL bottle)
propranolol ER (Innopran XL)	80 or 120 mg at bedtime	-	-	-	80, 120 mg capsules
propranolol ER (Inderal XL)	80 or 120 mg at bedtime	-	-	-	80, 120 mg capsules
propranolol LA	80 mg daily, then 120-160 mg daily	80-320 mg daily	-	See package insert for other indications	60, 80, 120, 160 mg capsules
sotalol	-	-	-	See package insert for other indications	80, 120, 160, 240 mg tablets
sotalol AF	-	-	-	See package insert for other indications	80, 120, 160 mg tablets
sotalol (Sotylize)	-	-	-	See package insert for other indications	5 mg/mL oral solution (250 mL, 480 mL bottle)
timolol	10-30 mg twice daily	-	-	MI: 10 mg twice daily See package insert for other indications	5, 10, 20 mg tablets

Combination Products

Drug	Initial Hypertension Dosage	Maximum Hypertension Dosage	Availability
atenolol / chlorthalidone (Tenoretic)[258]	50/25 mg once daily	100/25 mg once daily	50/25, 100/25 mg tablets
bisoprolol / hydrochlorothiazide (Ziac)[259]	2.5/6.25 mg once daily	20/12.5 mg once daily	2.5/6.25, 5/6.25, 10/6.25 mg tablets
metoprolol succinate / hydrochlorothiazide (Dutoprol)[260]	Individualized based on baseline and target blood pressure, as well as previous experience with antihypertensives	200/25 mg once daily (two 100/12.5 mg tablets)	25/12.5, 50/12.5, 100/12.5 mg tablets
metoprolol tartrate / hydrochlorothiazide (Lopressor HCT)[261]	50/25 mg twice daily	100/25 mg given as 1-2 tablets in a single or divided doses 100/50 mg given a single dose	50/25, 100/25, 100/50 mg tablets
nadolol / bendroflumethiazide (Corzide)[262]	40/5 mg once daily	80/5 mg once daily	40/5, 80/5 mg tablets
propranolol / hydrochlorothiazide (Inderide)[263]	40/25 mg twice daily	80/25 mg once or twice daily	40/25, 80/25 mg tablets

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included all agents in this class for the cardiovascular (CV) FDA-approved indications of hypertension, HF, angina, MI, and cardiac arrhythmia and comparative studies of nebivolol to other beta-blockers for hypertension. Very few comparative clinical trials in HF have been performed with agents in this class. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Angina

Head-to-head trials of FDA-approved beta-blockers for angina are lacking. Propranolol, which was the first beta-blocker, was shown to have efficacy in angina.[264] In very small trials, atenolol, metoprolol, and nadolol were shown to be as effective as propranolol in reducing anginal attacks and increasing exercise capacity.[265,266,267] Comparative studies of various beta-blockers have shown similar efficacy in angina.[268,269,270]

A double-blind, multicenter trial of 280 patients with stable angina randomized patients at week zero to metoprolol controlled-release 200 mg once daily or nifedipine 20 mg twice daily for six weeks; placebo or the alternative drug was then added for a further four weeks.[271] Exercise tests at week six showed both metoprolol and nifedipine increased the mean exercise time to 1-mm ST segment depression in comparison with week zero (both $p<0.01$). Metoprolol was more effective than nifedipine ($p<0.05$).

In a randomized, double-blind, three-month, multicenter study, carvedilol 25 to 50 mg twice daily was compared to metoprolol 50 to 100 mg twice daily in 368 patients with stable angina for antianginal and anti-ischemic efficacy.[272] Carvedilol improved the time to 1-mm ST-segment depression statistically significantly greater than metoprolol. Carvedilol at both doses was shown to be at least as safe and well tolerated as metoprolol at both doses.

Cardiac Arrhythmia

Head-to-head trials of FDA-approved beta-blockers for ventricular arrhythmias are lacking. Studies of carvedilol, bisoprolol, atenolol, nadolol, pindolol, and metoprolol have shown efficacy in controlling ventricular rate.[273,274,275,276]

Sotalol (Betapace, Sotylize) has been found to be effective in ventricular arrhythmias.[277,278] Sotalol AF (Betapace AF) has been studied in patients with symptomatic atrial fibrillation/atrial flutter (primarily paroxysmal atrial fibrillation/atrial flutter and patients with chronic atrial fibrillation) in randomized,

double-blind, multicenter, placebo-controlled trials. In the studies sotalol/AF prolonged the time to first recurrence of ECG-documented symptomatic atrial fibrillation/atrial flutter, and reduced the risk of recurrence for up to 12 months.[279] Safety and effectiveness of Sotilyze, the oral solution of sotalol, were based on oral sotalol tablets.

Heart Failure

carvedilol (Coreg)

U.S. Carvedilol Heart Failure Study: A double-blind, placebo-controlled study (n=1,094) evaluated carvedilol use in HF.[280] The primary endpoint was all-cause mortality with a secondary endpoint of cardiovascular morbidity (hospitalization). The population was mostly men with ischemic heart disease, NYHA Class II and III, with a LVEF ≤35 percent. Therapy with ACE inhibitors and diuretics for at least two months was required for inclusion in the study. Carvedilol was initiated at 6.25 mg twice daily (open-label). If tolerated, patients were randomized to carvedilol 12.5 mg twice daily or placebo in a double-blind manner. The target doses of carvedilol were 25 to 50 mg twice daily for six to 12 months. The trial was stopped early due to the carvedilol group having a 65 percent lower relative risk of death than the placebo group (p<0.001). Carvedilol patients had a 27 percent relative risk reduction in hospitalization for cardiac reasons (p=0.036). Worsening of HF was the most common reason for withdrawal from the study and was seen more frequently in the placebo group.

carvedilol in severe HF (COPERNICUS): In a double-blind study evaluating the use of carvedilol in severe chronic HF, 2,289 patients with LVEF <25 percent were randomized to carvedilol or placebo and evaluated for rates of hospitalizations and death.[281] Patients had symptoms at rest or with minimal exertion despite therapy with diuretics, ACE inhibitors, or ARBs. The carvedilol group had a 35 percent decrease in the relative risk of death over the placebo group in the mean 10.4-month study period (p=0.0014). The relative combined risk of death and hospitalization was reduced by 24 percent in the carvedilol group compared to the placebo group (p=0.00002). More patients withdrew from the study in the placebo group due to adverse effects or other reasons (p=0.02). An evaluation of carvedilol dose titration during the first eight weeks of therapy did not demonstrate an increase, but rather a decrease of deaths, hospitalizations, and numbers of patients withdrawing from the study, as compared to placebo.[282] Worsening of HF was similar in both groups (carvedilol 5.1 percent, placebo 6.4 percent).

carvedilol (Coreg) after MI with LVD (CAPRICORN): A trial enrolling 1,959 patients evaluated carvedilol in the setting of acute MI complicated by LVD.[283] In the multicenter, double-blind, placebo-controlled trial, patients with MI and LVEF ≤ 40 percent were randomized to carvedilol 6.25 mg twice daily or placebo. The primary outcomes were all-cause mortality or hospital admission for cardiac reasons. Eligible patients were receiving ACE inhibitors and diuretics. Therapy was titrated to a maximum of carvedilol 25 mg twice daily over four to six weeks. The mean follow-up was 1.3 years. All-cause mortality was lower in the carvedilol group compared to placebo (12 percent carvedilol, 15 percent placebo, 23 percent relative risk reduction; p=0.03). Atrial and ventricular antiarrhythmic effects by carvedilol have been observed in this population.[284]

carvedilol (Coreg) and metoprolol tartrate (Lopressor)

One hundred fifty patients with HF and LVEF <35 percent were randomized to double-blind treatment with either metoprolol or carvedilol.[285] When compared with metoprolol (average dose 124±55 mg/day), patients treated with carvedilol (49±18 mg/day) showed larger increases in LVEF at rest (+10.9 percent versus +7.2 percent, p=0.038) and in LV stroke volume and stroke work during exercise

(both p<0.05) after 13 to 15 months of treatment. Carvedilol produced greater decreases in mean pulmonary artery pressure and pulmonary wedge pressure, both at rest and during exercise, compared to metoprolol (all p<0.05). In contrast, the metoprolol group showed greater increases in maximal exercise capacity than the carvedilol group (p=0.035). Both drugs improved symptoms, submaximal exercise tolerance, and quality of life to a similar degree. After a mean of 23 months of follow-up, 21 patients in the metoprolol group and 17 patients in the carvedilol group died or underwent transplantation.

COMET was a randomized, double-blind trial comparing carvedilol and metoprolol tartrate in 3,029 patients with HF for effects on all-cause mortality.[286] Most patients were classified as NYHA Class II and III and were on diuretics, ACE inhibitors, or ARBs with optional treatment with digoxin and spironolactone. All patients had a history of a cardiovascular event within two previous years. The average LVEF was 26 percent at baseline. Baseline heart rates were identical between the groups. Patients were randomized to carvedilol 3.125 mg twice daily and titrated to 25 mg twice daily or metoprolol tartrate 5 mg twice daily and titrated to 50 mg twice daily. The target dose was achieved by 75 percent of carvedilol patients and 78 percent of metoprolol patients. The average daily dose was 42 mg for carvedilol and 85 mg for metoprolol tartrate. Patients were followed for a mean of 58 months. All cause mortality was 34 and 40 percent for carvedilol and metoprolol tartrate, respectively (p=0.0017); COMET demonstrated a 17 percent relative risk reduction in all-cause mortality with carvedilol. The annual mortality rate was 8.3 percent for carvedilol group and 10 percent for metoprolol tartrate. The secondary endpoint of all-cause mortality and all-cause hospitalization was similar between the two groups. Fewer carvedilol patients experienced cardiovascular death (p=0.0004).[287] After four months, carvedilol reduced heart rate by a mean of 13.3 beats per minute whereas metoprolol reduced heart rate by 11.7 beats per minute. After 16 months, heart rate was similar between the groups. Overall, 32 percent of patients in both groups withdrew from the study. A criticism of the study is the lack of possible dose equivalency with carvedilol having a higher dose and lower heart rate therefore possibly greater benefits than metoprolol tartrate.

An analysis of the COMET trial compared the effects of carvedilol and metoprolol tartrate on vascular events.[288] Vascular endpoints were cardiovascular death, stroke, stroke death, myocardial infarction, and unstable angina. MI was seen in 69 carvedilol and 94 metoprolol patients (hazard ratio 0.71, 95% CI, 0.52 to 0.97, p=0.03). Cardiovascular death and nonfatal MI combined were reduced by 19 percent in carvedilol versus metoprolol (hazard ratio 0.81, 95% CI, 0.72 to 0.92, p=0.0009). Unstable angina was seen in 56 carvedilol-treated patients versus 77 metoprolol-treated patients (hazard ratio 0.71, 95% CI, 0.501 to 0.998, p=0.049). Stroke was reported in 65 versus 80 patients receiving carvedilol and metoprolol, respectively (hazard ratio 0.79, 95% CI, 0.57 to 1.1, p=0.163). Stroke or MI combined occurred in 130 carvedilol-treated and 168 metoprolol-treated patients (hazard ratio 0.75, 95% CI, 0.6 to 0.95, p=0.015), and fatal MI or fatal stroke occurred in 34 patients on carvedilol versus 72 patients receiving metoprolol (hazard ratio 0.46, 95% CI, 0.31 to 0.69, p=0.0002). The results show carvedilol improves vascular outcomes compared to metoprolol; however, the possible lack of dose equivalency in the COMET trial must be taken into account.

The objective of GEMINI, a randomized, double-blind, parallel-group trial, was to compare metoprolol tartrate and carvedilol in patients with diabetes.[289] A total of 1,235 patients with diabetes aged 36 to 85 years (mean age 61 years) were enrolled in GEMINI at 205 sites in the United States. All participants in GEMINI had stage 1 or 2 HTN (systolic blood pressure, SBP, 130-179 mm Hg and diastolic blood pressure, DBP, 80-109 mm Hg), currently on an ACE inhibitor or ARB, and controlled type 2 diabetes

(baseline glycosylated hemoglobin, HbA1c, 6.5 to 8.5 percent and C-peptide >0.6 ng/mL). There were no significant differences in baseline characteristics between the two groups. Less than 10 percent of patients had a history of coronary artery disease. Patients were randomized to carvedilol 6.25 mg twice daily (titrated to a maximum of 25 mg twice daily) or metoprolol tartrate 50 mg twice daily (titrated to maximum of 200 mg twice daily) and followed for a maximum of 35 weeks. Open-label hydrochlorothiazide 12.5 mg followed by a dihydropyridine CCB was added, if needed, to achieve blood pressure targets. The primary outcome was the mean change from baseline HbA1c following five months of maintenance therapy. Based on last observation carried forward, the carvedilol group had a significant change from baseline HbA1c (-0.12 percent; p=0.006). A greater proportion of subjects on metoprolol than on carvedilol had increases in HbA1c of greater than 0.5 percent (30 versus 22 percent, respectively) or greater than one percent (14.2 versus seven percent, respectively). Since blood pressure control and mean heart rate use of antihypertensive and lipid-lowering medications were similar in the two treatment groups, the GEMINI investigators believe that these could not have accounted for differences in HbA1c. Subjects in the carvedilol group had improved insulin resistance, as measured by the homeostasis model assessment insulin resistance index (HOMA-IR) (p=0.04), and less microalbuminuria, as measured by urinary albumin/creatinine excretion rate, compared with the metoprolol group (p=0.003). Significantly fewer subjects on carvedilol developed new-onset microalbuminuria compared with those on metoprolol (6.6 versus 11.1 percent; odds ratio, 0.53; 95% CI, 0.3 to 0.93; p=0.05). The frequency of bradycardia was higher with metoprolol (p=0.007) which may be indicative of a lack of equivalent doses between the two agents. Diabetes worsened in more patients in the metoprolol group (p=0.07) with more patients withdrawing due to worsening glycemic control (p=0.04). Weight gain was higher with metoprolol (1.2 kg versus 0.2 kg, p<0.001).

metoprolol succinate ER (Toprol XL)

MERIT-HF trial: A double-blind, placebo-controlled study enrolled 3,991 patients with chronic HF (NYHA Class II-IV and LVEF <40 percent).[290] Patients were stabilized on optimal concomitant therapy including diuretics, ACE inhibitors, cardiac glycosides, and nitrates. At randomization, 41 percent of patients were NYHA Class II and 55 percent were NYHA Class III. Patients were started on 12.5 mg once daily of metoprolol succinate ER if NYHA Class III-IV or 25 mg once daily if NYHA Class II. Dose titration occurred over an eight-week period, if tolerated. The mean daily dose of metoprolol succinate ER at the end of the trial was 159 mg. The target dose of metoprolol succinate ER 200 mg daily was achieved in 64 percent of patients. The trial was terminated early (mean duration of one year) because of a 34 percent relative risk reduction in all-cause mortality.

Numerous subgroup analyses have found positive effects with metoprolol succinate ER in HF. In the MERIT-HF study, women (n=898) with NYHA III and IV were found to benefit from metoprolol succinate ER. A 21 percent relative risk reduction was noted in the combined endpoint of all-cause mortality and all-cause hospitalization for women (p=0.044).[291] The relative risk of hospitalization for worsening HF was also reduced by 42 percent in the metoprolol succinate ER group compared to placebo. The relative risk reduction in total mortality was also observed for hypertensive patients and for patients with severe HF randomized to metoprolol succinate ER.[292,293] In a subanalysis, metoprolol succinate ER provided benefits in black patients with clinically stable HF and LVD.[294]

The REversal of Ventricular Remodeling with Toprol-XL (REVERT) trial: In a randomized, controlled study, 149 patients with LVEF < 40 percent, mild left ventricular dilation, and no symptoms of heart failure (NYHA class I) received metoprolol succinate ER 200 mg, 50 mg, or placebo for 12 months.[295] At

one year, the metoprolol succinate ER 200 mg group showed a 14 +/- 3 mL/m^2 decrease (least square mean+/- SE) in end systolic volume index and a 6 +/-1 percent increase in left ventricular ejection fraction (p<0.05 versus baseline and placebo for both). In the metoprolol succinate ER 50 mg group, there were no statistical differences in end-systolic and end-diastolic volume indexes versus placebo; however, ejection fraction increased by 4 +/- 1 percent (p<0.05 versus baseline and placebo).

Hypertension

In the 1980s and 1990s, a number of head-to-head studies of beta-blockers found them to be similar in reducing blood pressure.[296,297,298,299,300] In addition, beta-blockers were compared to diuretics and were generally shown to be less effective in reducing cardiovascular events, as demonstrated in the MRC and HAPPHY trials.[301,302] The MAPHY trial, however, showed a lower all-cause mortality for metoprolol than a thiazide diuretic in relatively young white men aged 40 to 64 years old.[303] Beta-blockers have also been compared to other classes. The INVEST trial found atenolol and the calcium channel blocker verapamil to have the same effect on blood pressure reduction, and there was no difference in the primary endpoints.[304] More recently, there has been debate regarding the use of beta-blockers for primary prevention in hypertension.

ASCOT-BPLA: The trial was a randomized controlled, multicenter, trial of 19,257 patients with hypertension aged 40 to 79 years with at least three other CV risk factors.[305] Amlodipine 5 to 10 mg (adding perindopril 4 to 8 mg as required) or atenolol 50 to 100 mg (adding bendroflumethiazide 1.25 to 2.5 mg and potassium as required) were evaluated for the primary endpoint of non-fatal MI and fatal CHD. The study was stopped early after 5.5 years of median follow-up. The amlodipine group was associated with greater reduction in all-cause mortality. The amlodipine group had lower risk of stroke (HR 0.77, 95% CI 0.66 to 0.89, p=0.0003) and improved survival (HR 0.89, 95% CI 0.81 to 0.99, p=0.0247) compared to the atenolol group. Cardiovascular mortality was also lower in the amlodipine group (HR 0.76, 95% CI 0.65 to 0.9, p=0.001). Fewer patients in the amlodipine group met the primary endpoint, but this was not a statistically significant difference (p=0.1052).

LIFE: The study was a randomized, double-blind, parallel-group study of 9,193 patients aged 55 to 80 years with essential hypertension and LVH.[306] Patients were randomized to once daily losartan-based or atenolol-based antihypertensive treatment for at least four years and until 1,040 patients had a primary cardiovascular event (death, MI, or stroke). Both treatments effectively lowered blood pressure. Losartan reduced the primary outcome (13 percent greater than atenolol) as there was a 25 percent relative risk reduction of stroke risk (absolute risk reduction 4 percent, 27.9 percent for atenolol and 23.8 percent for losartan, p=0.021).

nebivolol (Bystolic) and atenolol

A 12-week, double-blind, randomized, multicenter study compared nebivolol to atenolol in 205 middle-aged patients with mild to moderate hypertension.[307] After a placebo run-in phase, patients received either nebivolol 5 mg daily or atenolol 100 mg daily. The primary endpoint of the study was the change in SBP and DBP from baseline. Both agents showed similar significant antihypertensive effects for SBP and DBP reduction (p<0.01 for all values). Sitting and standing heart rate values were significantly reduced by both agents. The bradycardic response induced by nebivolol treatment was significantly less than atenolol. Nebivolol demonstrated a better tolerability profile and a lower incidence of adverse effects.

A randomized, double-blind, parallel-group study compared once daily nebivolol 5 mg, atenolol 50 mg, and placebo in 366 patients with mild to moderate hypertension for four weeks.[308] There was a similar reduction in SBP and DBP compared to placebo for both agents. Both drugs were well tolerated.

A nine-month extension study of three, three-month, phase III double-blind, randomized trials showed patients receiving nebivolol monotherapy had decreases in DBP and SBP of 15 and 14.8 mm Hg, respectively.[309] More than 78 percent of patients were responders to nebivolol monotherapy, and 65 percent were responders to combination with a diuretic. Overall incidence of adverse events in the extension study was comparable to that seen in the feeder studies and decreased over time.

Myocardial Infarction

Head-to-head trials of beta-blockers in MI are lacking. Placebo comparative trials are described below. The CAPRICORN study with carvedilol is discussed in the CHF section.[310]

metoprolol

Goteborg: The Goteborg Metoprolol Trial, randomized 1,395 patients with suspected acute MI, on admission, to double-blind treatment with placebo or metoprolol (15 mg IV followed by 200 mg orally daily) for 90 days. Deaths occurred in 8.9 percent of placebo and 5.7 percent of metoprolol groups, a mortality reduction of 36 percent ($p<0.03$). After 90 days, all patients were recommended open treatment with metoprolol, and the difference in mortality between the two groups was maintained after one year. Early institution (within 12 hours) of metoprolol influenced infarct development during the first three days. Metoprolol reduced the incidence on fatal and nonfatal infarction by 35 percent, during the next four to 90 days. Fewer episodes of ventricular fibrillation were recorded in the metoprolol group versus placebo (six versus 17 patients). Therapies were well tolerated. A retrospective subgroup analysis of Goteborg found that, during the first year, mortality in the metoprolol group was 14 percent versus 27 percent among patients randomized to placebo ($p=0.0099$).[311] Patients randomized to placebo who showed signs of heart failure had a one year mortality rate of 28 percent compared with 10 percent for patients without signs of heart failure ($p<0.001$).

MIAMI: MIAMI was a randomized, double-blind, multicenter study of 5,778 patients with definite or suspected MI, evaluating the effect of metoprolol on mortality and morbidity.[312] Metoprolol (15 mg IV followed by 200 mg/day orally) or placebo was started shortly after the patient's arrival in hospital within 24 hours of the onset of symptoms, and continued for the study period (15 days). There was a 13 percent nonsignificant difference in the incidence of death between metoprolol and placebo ($p=0.29$). Metoprolol seemed to have most effect on mortality in patients with multiple risk factors who were at higher risk, when previously recorded risk indicators of mortality were retrospectively analyzed. These indicated that there was a category which showed higher risk which contained approximately 30 percent of all randomized patients. In these, the mortality rate in the metoprolol-treated group was 29 percent less than in the placebo group. In the remaining lower risk categories, there was no difference between the treatment groups. There was no significant effect on ventricular fibrillation, but the number of episodes was lower in the metoprolol group during days six through 15. The incidence of supraventricular tachyarrhythmias, the use of cardiac glycosides and other antiarrhythmics, and the need for pain-relieving treatment were significantly diminished by metoprolol amongst all randomized patients. Treatments were well tolerated.

timolol

Norwegian Multicenter Study: A randomized, double-blind, placebo-controlled, multicenter study compared timolol 10 mg twice daily with placebo for reduction in mortality and reinfarction.[313] Treatment was started seven to 28 days after infarction in 1,884 patients and followed for a mean of 17 months. When deaths that occurred during treatment or within 28 days of withdrawal were considered, the cumulated sudden-death rate over 33 months was 13.9 percent in placebo versus 7.7 percent in the timolol group, a reduction of 44.6 percent (p=0.0001). The cumulated reinfarction rate was 20.1 percent in placebo and 14.4 percent in the timolol group (p=0.0006). A six-year follow-up showed a cumulative mortality rate of 32.3 percent in placebo and 26.4 percent in the timolol group (p=0.0028).[314]

propranolol

BHAT: The beta-Blocker Heart Attack Trial (BHAT) was a randomized, double-blind, placebo-controlled, multicenter study.[315] The primary endpoint was reduction in total mortality during a two- to four-year period. BHAT randomized 3,837 patients with a prior MI to either propranolol or placebo, five to 21 days after the infarction. Depending on serum drug levels, the dose of propranolol was either 180 or 240 mg/day. The trial was stopped nine months early. Total mortality during the average 24-month follow-up period was 7.2 percent in the propranolol group and 9.8 percent in the placebo group. Arteriosclerotic heart disease (ASHD) mortality was 6.2 percent in the propranolol group and 8.5 percent in the placebo group. Sudden cardiac death, a subset of ASHD mortality, was 3.3 percent among the propranolol patients and 4.6 percent among the placebo patients. Serious adverse effects were uncommon. A retrospective subgroup analysis of BHAT found that the incidence of heart failure after randomization and during the study was 6.7 percent in both groups so heart failure did not change propranolol's effect on total mortality.[316]

META-ANALYSIS

A systematic review between January 1966 and January 1998 identified ten trials involving a total of 16,164 hypertensive elderly patients (≥ 60 years) and assessed antihypertensive efficacy of beta-blockers (mostly atenolol trials) and their effects on CV morbidity and mortality and all-cause morbidity compared with diuretics.[317] Diuretic therapy was superior to beta-blockade with regard to all endpoints and was effective in preventing cerebrovascular events (OR, 0.61; 95% CI, 0.51 to 0.72), fatal stroke (OR, 0.67; 95% CI, 0.49 to 0.9), CHD (OR, 0.74; 95% CI, 0.64 to 0.85), CV mortality (OR, 0.75; 95% CI, 0.64 to 0.87), and all-cause mortality (OR, 0.86; 95% CI, 0.77 to 0.96). In contrast, beta-blocker therapy only reduced the odds for cerebrovascular events (OR, 0.75; 95% CI, 0.57 to 0.98) but was ineffective in preventing CHD, CV mortality, and all-cause mortality (ORs, 1.01, 0.98, and 1.05, respectively).

A meta-analysis evaluated the effect of atenolol on cardiovascular morbidity or mortality in patients with primary hypertension in 17,671 patients.[318] Four studies that compared atenolol with placebo or no treatment, and five that compared atenolol with other antihypertensive drugs (half from the LIFE study) were identified. Despite major differences in blood pressure lowering, there were no outcome differences between atenolol and placebo in the four studies, on all-cause mortality (relative risk 1.01 [95% CI 0.89 to 1.15]), cardiovascular mortality (0.99 [0.83 to 1.18]), or MI (0.99 [0.83 to 1.19]). The risk of stroke, however, tended to be lower in the atenolol group than in the placebo group (0.85 [0.72 to 1.01]). When atenolol was compared with other antihypertensives, there were no major differences in

blood pressure reduction between the treatment arms. There was a significantly higher all-cause mortality (1.13 [1.02 to 1.25]) with atenolol than with other active treatment. Stroke was also more frequent with atenolol treatment (relative risk 1.3).

A meta-analysis of 13 randomized controlled trials compared primary prevention of beta-blockers to other antihypertensive classes, in 105,951 patients.[319] The relative risk of stroke was 16 percent higher for beta-blockers (95% CI, 4 to 30 percent) than for other agents. There was no difference for MI. Beta-blockers did reduce the risk of stroke compared with placebo or no treatment; the relative risk of stroke was reduced by 19 percent for all beta-blockers (7 to 29 percent), which is about half that expected from prior hypertension trials. There was no difference for MI or mortality. A re-analysis of this meta-analysis and when more trials were included, in older patients (≥ 60 years) beta-blockers had a higher risk of stroke (RR 1.18, 95% CI 1.07 to 1.3) compared to other drugs.[320] There were no differences between beta-blockers and other drug classes in younger patients (< 60 years) in the composite outcome of death, MI, or stroke).

A Cochrane database systematic review included 13 randomized controlled trials of 91,561 patients and compared beta-blockers to placebo or no treatment (four trials with 23,613 patients), diuretics (five trials with 18,241 patients), calcium-channel blockers (CCB) (four trials with 44,825 patients), and renin-angiotensin system (RAS) inhibitors (three trials with 10,828 patients).[321] The risk of all-cause mortality was not different between first-line beta-blockers and placebo, diuretics, or RAS inhibitors, but was higher for beta-blockers compared to CCBs (RR 1.07, 95% CI, 1 to 1.14). The risk of total cardiovascular disease (CVD) was lower for first-line beta-blockers compared to placebo (RR 0.88, 95% CI, 0.79 to 0.97). This is due to the significant decrease in stroke (RR 0.8, 95% CI, 0.66 to 0.96); coronary heart disease (CHD) risk was not significantly different between beta-blockers and placebo. The effect of beta-blockers on CVD was significantly compared to CCBs (RR 1.18, 95% CI, 1.08 to 1.29), but was not significantly different from diuretics or RAS inhibitors. Increased total CVD was due to an increase in stroke versus CCBs (RR 1.24, 95% CI, 1.11 to 1.4).There was also an increase in stroke with beta-blockers compared to RAS inhibitors (RR 1.3, 95% CI, 1.11 to 1.53). There was no significant difference in CHD between beta-blockers and diuretics or CCBs or RAS inhibitors. Patients on beta-blockers were more likely to discontinue treatment due to adverse events than with diuretics (RR 1.86, 95% CI, 1.39 to 2.5) and RAS inhibitors (RR 1.41, 95% CI, 1.29 to 1.54), but there was no significant difference with CCBs. Seventy five percent of patients in these studies used atenolol. Differential effects on age or race were not explored.

A Cochrane database systematic review included 24 randomized trials (n=58,040) of at least one year duration comparing one of six major drug classes with a placebo or no treatment.[322] Thiazides (19 RCTs) reduced mortality (RR 0.89, 95% CI, 0.83 to 0.96), stroke (RR 0.63, 95% CI, 0.57 to 0.71), CHD (RR 0.84, 95% CI, 0.75 to 0.95) and CV events (RR 0.7, 95% CI, 0.66 to 0.76). Low-dose thiazides (8 RCTs) reduced CHD (RR 0.72, 95% CI, 0.61 to 0.84), but high-dose thiazides (11 RCTs) did not (RR 1.01, 95% CI, 0.85 to 1.2). Beta-blockers (5 RCTs) reduced stroke (RR 0.83, 95% CI, 0.72 to 0.97) and CV events (RR 0.89, 95% CI, 0.81 to 0.98), but not CHD (RR 0.9, 95% CI, 0.78 to 1.03) or mortality (RR 0.96, 95% CI, 0.86 to 1.07). ACE inhibitors (3 RCTs) reduced mortality (RR 0.83, 95% CI, 0.72 to 0.95), stroke (RR 0.65, 95% CI, 0.52 to 0.82), CHD (RR 0.81, 95% CI, 0.7 to 0.94), and CV events (RR 0.76, 95% CI, 0.67 to 0.85). CCBs (1 RCT) reduced stroke (RR 0.58, 95% CI, 0.41 to 0.84) and CV events (RR 0.71, 95% CI, 0.57 to 0.87), but not CHD (RR 0.77, 95% CI, 0.55 to 1.09) or mortality (RR 0.86, 95% CI, 0.68 to 1.09). No RCTs were found for ARBs or alpha-blockers.

A meta-analysis of nine studies evaluated the effect of heart rate reduction on CV outcomes in 34,096 patients with hypertension with a mean age of 58 years.[323] Paradoxically, the slower the heart rate the greater the risk of CV outcomes and death. A lower heart rate was associated with a greater risk for the endpoints of all-cause mortality (r=-0.51; p<0.0001), cardiovascular mortality (r=-0.61; p<0.0001), myocardial infarction (r=-0.85; p<0.0001), stroke (r=-0.2; p=0.06), or heart failure (r=-0.64; p<0.0001). The same was true when the heart rate difference between the two treatment modalities at the end of the study was compared with the relative risk reduction for cardiovascular events.

A meta-analysis of 12 randomized controlled trials evaluated 112,177 hypertensive patients for primary prevention of heart failure. Beta-blockers reduced blood pressure compared to placebo, resulting in a 23 percent (trend) reduction in HF risk (p=0.055).[324] When compared with other agents, the antihypertensive efficacy of beta-blockers was comparable, which resulted in similar but no incremental benefit for HF risk reduction in the overall cohort (risk ratio: 1; 95% CI, 0.92 to 1.08), in the elderly (≥ 60 years) or in the young (<60 years). Analyses of secondary outcomes showed that beta-blockers confirmed similar but no incremental benefit for the outcomes of all-cause mortality, cardiovascular mortality, and myocardial infarction. Beta-blockers increased stroke risk by 19 percent in the elderly (p<0.0001) yet decreased the risk of stroke in the young by 22 percent compared to other antihypertensives.

A meta-analysis of randomized controlled trials compared beta-blockers, calcium channel blockers (CCBs), and nitrates for angina.[325] Rates of cardiac death and MI were not significantly different for beta-blockers versus CCBs (OR, 0.97; 95% CI, 0.67 to 1.38; p=0.79). Beta-blockers were discontinued due to adverse events less often than CCBs (OR, 0.72; 95% CI, 0.6 to 0.86; p<0.001). Too few trials compared nitrates with calcium antagonists or beta-blockers to draw firm conclusions about relative efficacy.

Two meta-analyses reviewed the use of beta-blockers post MI and found a significant mortality reduction.[326,327] A meta-analysis of beta-blocker use post MI found that the relative benefit of beta-blockers on mortality after a MI is similar in the presence or absence of heart failure.[328]

A meta-analysis of randomized controlled trials of beta-blockers after acute MI found 10 percent of 54,234 patients randomized to beta-blockers or control died.[329] The review identified a 23 percent reduction in the odds of death in long term trials (95% CI, 15 to 31 percent), but only a four percent reduction in the odds of death in short term trials (-8 to 15 percent). Meta-regression in long term trials did not find a significant difference in effectiveness in drugs with cardioselectivity but did identify an almost significant trend towards decreased benefit in drugs with intrinsic sympathomimetic activity (ISA). The most evidence was available for propranolol, timolol, and metoprolol.

A meta-analysis of 12 randomized controlled studies investigated the efficacy and tolerability of nebivolol compared with other antihypertensive drugs and placebo in patients with hypertension.[330] Antihypertensive response rates (the percentage of patients achieving target BP levels or a defined DBP reduction) were higher with nebivolol than with ACE inhibitors (OR 1.92; p=0.001) and all antihypertensive drugs combined (OR 1.41; p=0.001) and similar to beta-blockers, calcium channel blockers (CCBs), and the angiotensin receptor blocker (ARB), losartan. More patients on nebivolol achieved target BP levels compared with patients treated with losartan (OR 1.98; p=0.004), CCBs (OR 1.44; p=0.024), and all antihypertensive drugs combined (OR 1.35; p=0.012). The percentage of patients experiencing adverse events did not differ between nebivolol and placebo; adverse event rates were significantly lower with nebivolol than losartan (OR 0.52; p=0.016), other beta-blockers (OR

0.56; p=0.007), nifedipine (OR 0.49; p<0.001), and all antihypertensive drugs combined (OR 0.59; p<0.001).

A meta-analysis to evaluate the efficacy of sotalol in the prevention of postoperative supraventricular tachyarrhythmias was performed.[331] A systematic review produced 15 eligible publications that provided 20 comparisons of sotalol with a control group. The incidence and relative risk (RR) with 95% confidence interval (CI) of developing postoperative supraventricular tachyarrhythmias while taking sotalol were, sotalol (n=489) versus placebo (n=499): 22.5 versus 41.5 percent, RR=0.55 (CI, 0.454-0.667, p<0.001); sotalol (n=304) versus no treatment (n=311): 12 versus 39 percent, RR=0.329 (CI, 0.236-0.459, p<0.001); sotalol (n=488) versus beta-blocker (n=555): 14 versus 23 percent, RR=0.644 (CI, 0.495-0.838, p<0.001); sotalol (n=139) versus amiodarone (n=146): no significant differences in supraventricular tachyarrhythmia prevention; and sotalol (n=51) versus magnesium (n=54): no significant differences in supraventricular tachyarrhythmia prevention. Whether sotalol is administered orally or intravenously did not significantly affect efficacy. Initiating sotalol after surgery (as opposed to preoperatively) showed a trend toward less adverse events (before: RR=1.700 [CI, 0.903-3.200] and after: RR=0.767 [CI, 0.391-1.505]).

SUMMARY

Beta-blockers have similar efficacy for the treatment of hypertension (HTN). The role of beta-blockers in primary prevention for hypertension has been questioned. The 2014 JNC-8 HTN guidelines and the 2013 AHA/ACC/CDC HTN scientific advisory recommend diuretics as first line for pharmacotherapy. If elevated blood pressure persists, combination therapy is warranted.

Beta-blockers are equally effective in treating stable angina. The 2007 ACC/AHA chronic stable angina guidelines recommend indefinite beta-blocker therapy for blood pressure control in patients with coronary artery disease (CAD), and in all patients who have had myocardial infarction (MI), acute coronary syndrome (ACS), or left ventricular dysfunction (LVD), with or without heart failure symptoms. Beta-blockers without intrinsic sympathomimetic activity (ISA) are preferred, since those with ISA may not decrease heart rate and blood pressure at rest.

Beta-blockers reduce morbidity and mortality and are considered the standard of care in patients with a prior MI. The 2014 ACC/AHA guidelines for Non-ST Coronary Syndromes and the ACCF/AHA 2013 STEMI guidelines recommend indefinite beta-blocker therapy in all hemodynamically stable patients with unstable angina and MI. The 2007 AHA HTN guidelines in ischemic heart disease prefer cardioselective beta-blockers without ISA in these patients.

Bisoprolol (Zebeta), metoprolol succinate ER (Toprol XL), and carvedilol (Coreg, Coreg CR) all have clinical data to support their use in the management of HF; however, only metoprolol succinate ER and carvedilol are FDA-approved for heart failure. The 2013 ACC/AHA HF guidelines recommend using one of the following beta-blockers for HF: bisoprolol, carvedilol, or metoprolol succinate ER.

Ventricular arrhythmias contribute to the increased risk for sudden cardiac death in patients with HF and MI. The 2006 ACC/AHA/ESC guidelines for ventricular arrhythmias and prevention of sudden cardiac death recommend beta-blockers as standard of care.

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